SUMMARY OF INSTRUCTIONS

Study of Tick Bite-Associated Rash Lesions of Unknown Etiology in the Southern United States (STARI)

Does the patient meet the case definition?

A person with acute onset (within 14 days of visit to physician's office) of an annular, erythematous, expanding rash that attains a size of at least 5 cm in diameter, when no alternative explanation for the rash can be found, AND

A history of tick bite or potential exposure to ticks within 14 days before the onset of the rash.

Obtain study documents and materials

These include physician instructions, informed consent forms, unaffiliated investigator form and Belmont Report, laboratory submission and DASH forms, and specimen collection kit from CDC (if desired).

Complete Unaffiliated Investigator Form

Send or FAX it to Ms. Constance Bonds, as specified.

Informed consent

If patient consents to be in this research study, ask patient to read and sign appropriate consent /assent forms IN DUPLICATE (two copies have been provided).

For detailed guidance about informed consent requirements for minors, see page 2 of instructions.

Patient should keep ONE COPY of informed consent/assent for minors; SECOND COPY should be sent to CDC, as below.

Collect specimens as directed in Instructions for Physicians

Do NOT biopsy facial or neck lesions.

Complete laboratory submission form

Also complete optional Data and Specimen Handling Form (CDC "DASH" form) to request serology for Lyme disease.

Ship to CDC: 2nd copy of signed informed consent/assent forms, laboratory submission form, optional DASH form, and specimens to CDC by overnight Federal Express using enclosed CDC Federal Express shipping form. **We cannot reimburse you for shipping costs if you ship without using the CDC account number.**

Questions? See Physician Instructions, or contact Drs. Barbara Johnson (970) 221-6463, e-mail bjohnson@cdc.gov; Jacob Kool (970) 266-3540, e-mail jkool@cdc.gov; or Paul Mead (970) 221-6474, e-mail pmead@cdc.gov .

Physician Instructions for Collecting and Handling Clinical Specimens and Data

Study of Patients with Tick Bite-Associated Rash Lesions of Unknown Etiology in the Southern United States

Background

Lyme disease is due to infection with the tick-transmitted spirochete, *Borrelia burgdorferi*. In the United States, the regions with the highest incidences of Lyme disease are the Northeast, Upper Midwest, and northern Pacific Coast. The characteristic annular, macular, erythematous skin lesion of early Lyme disease, erythema migrans (EM), occurs at the site of the infected tick bite, has an incubation period of 3-31 days, and typically expands over time, sometimes to a diameter of $30 cm.

Tick bite-associated EM-like lesions also occur in the southern United States, but the etiology of such lesions is unknown. Some appear to be associated with bites of the Lone Star tick, *Amblyomma americanum*, which is the most common human-biting tick in the region. Studies to date have failed to convincingly implicate *B. burgdorferi* as the cause of the rash. Possible etiologies include a novel tick-transmitted spirochete, called *Borrelia lonestari*, another infectious agent, or some other inflammatory process.

To determine the etiology and epidemiology of tick-associated annular skin lesions in the South, scientists at the Centers for Disease Control and Prevention (CDC) are cooperating with clinicians to collect appropriate clinical material for research purposes. Skin specimens will be tested by polymerase chain reaction (PCR) for *Borrelia* DNA sequences and evaluated by microscopy. Once tick cell culture methods have been established at CDC, a portion of each skin and blood sample will be co-cultured with tick cells in an attempt to isolate *B. lonestari.* Serum samples will not be tested immediately, but will be stored in a confidential manner until serologic tests for antibodies to *B. lonestari* have been developed. Portions of each type of sample will be stored to permit future testing of various etiologic hypotheses, once test methods are available. Future tests on these specimens will be identified to the CDC IRB and approved by the IRB as an amendment to this protocol before they are performed. Research subjects and unaffiliated investigators will not be informed of these test results.

Your cooperation is important to insure that informed patient consent is obtained, appropriate clinical specimens are obtained and properly handled, and that standardized and complete clinical data are collected. Please read carefully the following guidelines and any enclosures or attachments. If you have technical questions, wish to inquire about the availability of supplies for specimen collection, or wish to have copies of pertinent publications in the scientific literature, please contact one of the CDC scientists listed below.

Patient Eligibility

The following criteria should be used to determine if a patient is eligible for enrollment:

1. A person at least three years old with acute onset (within 14 days of visit to a physician's office) of an annular, erythematous, expanding EM-like rash that attains a size of at least 5 cm in diameter, when no alternative explanation for the rash can be found, and with

2. A history of tick bite at the rash site or potential exposure to ticks within 14 days prior to rash onset, and with

3. A willingness to consent to storage of all biologic samples that are donated for future laboratory testing. An amended IRB protocol will be submitted for review of any proposed additional testing. Such tests will not be performed until the amended protocol is approved.

Your participation

If you wish to be a collaborating physician, please read a summary of the ethical principles and guidelines for the protection of human subjects of research known as the *Belmont Report*, which is in this study packet. Please then read and sign the Unaffiliated Investigator Agreement (UIA) indicating that you will protect the rights and welfare of human subjects involved in research under this CDC Institutional Review Board (IRB)-approved protocol. **You must sign and return the UIA or you may not submit specimens.**

Informed Consent for adults and Assent forms for minors

1. Adult patients: PRIOR to collecting specimens, please ask adult patients who are legally able to give consent to read and sign the Adult Consent/ Parental Permission/ Adolescent Assent form.
2. Patients between 15 and 17 years old: A parent or guardian should give permission by signing an Adult Consent/ Parental Permission/ Adolescent Assent form and the minor child should give assent by signing another copy of the Adult Consent/ Parental Permission/ Adolescent Assent form.
3. Patients between 7 and 14 years old: A parent or guardian should give permission by signing an Adult Consent/ Parental Permission/ Adolescent Assent form and the minor child should give assent by signing a Child's Assent form for Minors.
4. Patients between 3 and 7 years old: We will enroll children older than 3 with the permission of a parent or guardian. An Adult Consent/ Parental Permission/ Adolescent Assent form signed by a legally responsible adult is sufficient for enrollment of a child aged 3-7.

It is extremely important that your office return the signed and witnessed form(s) with the clinical specimens. **We cannot accept specimens and enroll patients in the study without signed informed consent and, when appropriate, an assent form for minors.**

Laboratory Submission Form for Data Collection

Please carefully complete the attached *Laboratory Submission Form for Southern Tick-Associated Rash Illness (STARI) Specimens.* Do not include the patient's name on the form. If possible, take a color photograph of the skin lesion, label it, and attach it to the Laboratory Submission form or submit a digital picture by e-mail to bjj1@cdc.gov. [Note: Clinical information that is legible and as complete as possible must accompany all specimens.]

If you wish to request standard serologic tests for Lyme disease, please also submit the enclosed CDC DASH form with the patient's name. Results of standard tests will be sent to you and to your state health department.

Clinical Specimen Collection and Handling

Ideally, the following samples should be collected. A specimen collection kit can be sent to your office prior to the beginning of tick season, or by overnight delivery service at the time a patient presents for care.

1) Two skin biopsy specimens, although one sample is valuable (see submission form).
2) Clotted blood for serum (acute-phase specimen now and a convalescent-phase specimen 3-6 weeks later)
3) Anti-coagulated whole blood

If a patient does not consent to a skin biopsy, it is still important to collect and submit the blood specimens and the clinical data. Please ask the patient or guardian to schedule an appointment 3-6 weeks from the initial visit on the day that the acute-phase blood samples are collected. Collect a convalescent-phase serum sample at the second visit. If the patient misses the second appointment, please call the patient at home to reschedule the serum collection.

Skin biopsies

NOTE: Please exclude persons with hemophilia or other coagulopathies, including patients taking potent anticoagulants such as warfarin. (Patients taking NSAIDs alone need not be excluded.) Also, please exclude immunocompromised patients and persons who are receiving chemotherapy. ***Do not biopsy facial or neck lesions for this study.***

To collect the one, or preferably two, skin biopsy specimens, use a standard sterile 2-mm punch instrument and sterile technique. Ideally, samples should be taken from 4-6 mm inside the outer margin of the annular EM-like skin lesion and within 2.5 cm of each other and to a depth of 3-4 mm. The biopsy sites should be anesthetized (0.5 ml of a 1% solution of lidocaine and epinephrine 1:100,000 at each site) and then disinfected with a tincture of iodine followed by an alcohol swab. Gently twist the punch instrument to cut the skin to a depth of only 3-4 mm. Remove the punch instrument and repeat for the second biopsy. Grasp each skin sample with fine-tipped forceps, pull it gently away from the body, and snip it at its base with iris scissors. If necessary, place the samples on a sterile gauze patch momentarily while attending to hemostasis. Hemostasis is usually achieved by pressure alone; a butterfly bandage or single nonabsorbable suture can be applied if necessary. Place one biopsy specimen into phosphate-buffered saline (tube enclosed) and refrigerate it. Place a second specimen, when available, into Streck tissue fixative (tube enclosed) and store it at room temperature. Both skin samples should be shipped on a gel-type ice pack (see below).

Instruct patients in the proper care of their skin biopsy site. Provide a copy of the wound care instruction sheet to each research subject or guardian.

If only one biopsy specimen is obtained, please place it in PBS transport medium.

Phlebotomy

Disinfect phlebotomy site(s) with a tincture of iodine followed by an alcohol swab. To minimize the risk of hematoma, apply direct pressure to phlebotomy site(s) with the arm straight and elevated for 3-4 minutes.

Clotted blood for serum

Collect a 10-ml acute-phase blood sample in the enclosed standard red/gray-topped serum separator tube and centrifuge it in the standard fashion. Store the sample at approximately 4EC and ship it to CDC on a gel-type ice pack. It is unnecessary to decant the serum from the clot after centrifugation. It is important that a convalescent-phase sample be collected 3-6 weeks later in a similar fashion and shipped on a gel-type ice pack.

If, in your judgment, less than a full 10-ml sample from a child is more appropriate, please collect only this lesser amount.

Uncoagulated whole blood

Collect a 5-ml blood sample in an EDTA-coated (purple-topped) tube in the standard fashion. Store it at approximately 4EC and ship it on a gel-type ice pack.

If, in your judgment, less than a full 5-ml sample from a child is more appropriate, please collect only this lesser amount.

Shipping and Reimbursement

CDC will pay for overnight shipping if you ask for a CDC Federal Express account number from one of the

CDC scientists listed below. **Reimbursement is not possible if you pay for shipping.**

CDC will pay fees for phlebotomy and skin biopsy procedures, if arranged in advance. Skin biopsy expenses should not be charged to participants, since this procedure is not routine for evaluation of rash illness.

Patients will not be paid for their participation.

Ship samples to:

Bacterial Zoonoses Branch
CDC
Foothills Campus (Rampart Road)
Fort Collins, CO 80521-2087
ATTN: Mr. Steve Sviat
(970) 221-6400

CDC Scientist Contacts

Dr. Barbara Johnson (Microbiology and Pathogenesis Laboratory)
Tel (970) 221-6463, E-mail bjohnson@cdc.gov

Dr. Jacob Kool (Epidemiology Activity)
Tel (970) 266-3540, E-Mail jkool@cdc.gov

Dr. Paul Mead (Epidemiology Activity)
Tel (970) 221-6474, E-mail pmead@cdc.gov

Bacterial Zoonoses Branch
Division of Vector-Borne Infectious Diseases
CDC
P.O. Box 2087
Fort Collins, CO 80522-2087

Wound Care Instruction Sheet
Southern Tick-Associated Rash Illness (STARI) Study

The small wound (less than 1/10th of an inch) that you have because you donated a skin sample should heal within a week or less. It is important to keep your wound clean and dry to promote healing.

1) Leave the Band-Aid and antiseptic ointment on for 48 hours, then remove it.
2) If your Band-Aid becomes wet or dirty in the first 48 hours, replace it with a clean one.
3) If your wound becomes dirty, wash it with mild soap, dry it, and apply a new Band-Aid.
4) Look at your wound two or three time per day to see if it shows signs of infection. An increase or spreading of redness is one sign of infection. Another sign is fluid draining from the area.
5) If you think that your wound has become infected, contact this office for advice.

Unaffiliated Investigator Agreement

Please complete and sign the attached **Unaffiliated Investigator Agreement** (UIA) form. The documents referenced in the UIA can be found at:

http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

If you are going to start consenting and/or collecting data from participants immediately, please **FAX** a copy of the completed and signed form to the attention of **Ms. Constance M. Bonds** at **404-371-5988.** Mail the original completed/signed UIA form to Ms. Bonds as soon as possible at the address below.

If you are not going to start consenting and collecting data immediately, mail the original completed/signed form to this address.

Ms. Constance M. Bonds
Assurance Coordinator
Human Research Protection Office
Centers for Disease Control and Prevention
1600 Clifton Rd. NE, (m/s D-73)
Atlanta, GA. 30033

Once the original signed form is received by Ms. Bonds at the CDC, she will sign the form and mail a copy to the CDC investigator to keep. The CDC investigator will then forward a copy for your protocols files.

Unaffiliated Investigator Agreement

Name of Institution Providing IRB Oversight: Centers for Disease Control and Prevention (CDC)

OHRP Federal-wide Assurance Number: FWA00001413

Unaffiliated Investigator's Name: _____

CDC Protocol number and title: **Protocol 4278, A Study to Determine the Etiology of Southern Tick-Associated Rash Illness (STARI) in the United States**

(1) The above-named Unaffiliated Investigator has reviewed: 1) The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (or other internationally recognized equivalent; see B1 of FWA Terms for institutions outside the United States); 2) the U.S. Department of Health and Human Services (DHHS) regulations for the protection of human subjects at 45 CFR 46 (or other internationally recognized equivalent, see B3 of FWA Terms for institutions outside the United States); 3) the Federalwide Assurance (FWA) referenced above; and 4) the relevant institutional policies and procedures for the protection of human subjects.

(2) The Investigator understands and hereby accepts the responsibility to comply with the standards and requirements stipulated in the above documents and to protect the rights and welfare of human subjects involved in research conducted under this Agreement.

(3) The Investigator will comply with all other National, State, or local laws or regulations that may provide additional protection for human subjects.

(4) The Investigator will abide by all determinations of the IRB/IEC designated under the above Assurance and will accept the final authority and decisions of the IRB/IEC, including but not limited to directives to terminate participation in designated research activities.

(5) The Investigator will complete any educational training required by the Institution and/or the IRB/IEC prior to initiating research covered under this Agreement.

(6) The Investigator will report promptly to the IRB/IEC any proposed changes in the research conducted under this Agreement. The investigator will not initiate changes in the research without prior IRB/IEC review and approval, except where necessary to eliminate apparent immediate hazards to subjects.

(7) The Investigator will report immediately to the IRB/IEC any unanticipated problems involving risks to subjects or others in research covered under this Agreement.

(8) The Investigator will obtain, document, and maintain records of informed consent from each subject or the subject's legally authorized representative as required under DHHS and FDA regulations (or other international or national equivalent) and stipulated by the IRB/IEC.

(9) The Investigator acknowledges and agrees to cooperate in the IRB/IEC's

responsibility for initial and continuing review, record keeping, reporting, and certification. The Investigator will provide all information requested by the IRB/IEC in a timely fashion.

(10) In conducting research involving FDA-regulated products, the Investigator will comply with all applicable FDA regulations and fulfill all investigator responsibilities (or investigator-sponsor responsibilities, where appropriate), including those described at 21 CFR 312 and 812.

(11) The Investigator will not enroll subjects in research under this Agreement prior to its review and approval by the IRB/IEC.

(12) Emergency medical care may be delivered without IRB/IEC review and approval to the extent permitted under applicable Federal regulations and State law. However, data and information obtained as a result of emergency medical care may not be included as part of federally-supported or –conducted research.

(13) This Agreement does not preclude the Investigator from taking part in research not covered by the Agreement.

(14) The Investigator acknowledges that he/she is primarily responsible for safeguarding the rights and welfare of each research subject, and that the subject's rights and welfare must take precedence over the goals and requirements of the research.

Investigator Signature: _____Date:_____

Printed Name: _____ Degree(s): _____
(Last) (First) (Middle Initial)

Phone Number: _____

Address: _____

_____
(City) (State/Province) (Zip/Country)

IRB/IEC Institutional Official

Signature: _____ Date: _____

Ms. Constance M. Bonds
Assurance Coordinator
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1600 Clifton Rd. NE, (m/s D-73)
Atlanta, GA. 30033

Telephone: 404- 371-5259
FAX: 404- 371-5988
E-mail: ahsubjects@cdc.gov

PROTECTION OF HUMAN SUBJECTS

BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH

Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Table of Contents

Summary

On July 12, 1974, the National Research Act (Public Law 93348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects, and to develop guidelines, which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (I) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research, and (iv) the nature and definition of informed consent in various research settings. *The Belmont Report* attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center, supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of institutional review boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists, who assisted the Commission in fulfilling this part of its

charge, is available as DHEW Publication No. (OS) 780013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, *The Belmont Report* does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that *The Belmont Report* be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.
Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
Dorothy I. Height, President, National Council of Negro Women, Inc.
Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.
Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
*David W. Louisell, J. D., Professor of Law, University of California at Berkeley.
Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.
Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.
*Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.

* Deceased.

THE BELMONT REPORT

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg Code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This Code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in

research involving human subjects. These principles cannot always be applied, so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects. This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred, partly because both often occur together (as in research designed to evaluate a therapy), and partly because notable departures from standard practice are often called "experimental", when the terms "experimental" and "research" are not carefully defined. For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental" in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage, in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. Research and practice may be carried on together, when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is, that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

Respect for Persons

Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy, and the requirement to protect those with diminished autonomy. An autonomous person is an individual capable of deliberation about personal goals, and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices, while refraining from obstructing their actions, unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so. However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part, because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated. Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm, and the likelihood of benefit. Them judgment that any individual lacks autonomy should be periodically reevaluated, and will vary in different situations. In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities, for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

Beneficence

Persons are treated in an ethical manner, not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm; and (2) maximize possible benefits, and minimize possible harms. The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person, regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment". Learning what will in fact

benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks. The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge, and from the development of novel medical, psychotherapeutic, and social procedures. The principle of beneficence often occupies a well-defined, justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children --even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that, on closer investigation, turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk, without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out, that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

Justice

Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved". An injustice occurs, when some benefit to which a person is entitled is denied without good reason, or when some burden is imposed unduly. Another way of conceiving the principle of justice is that, equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property, on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit. Questions of justice have long been associated with social practices, such as punishment, taxation and political representation. Until recently, these questions have not generally been associated with scientific research. However, they are foreshadowed, even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries, the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was

condemned as a particularly vagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected, simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them, and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk benefit assessment, and the selection of subjects of research.

Informed Consent

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided, when adequate standards for informed consent are satisfied. While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information

Most codes of research establish specific items for disclosure, intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate, since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient, since the research subject, being in essence a volunteer, may wish to know considerably more about risks

gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be, that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk, and the voluntary nature of participation. A special problem of consent arises, where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research, of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified, only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases, in which disclosure would destroy or invalidate the research, from cases in which disclosure would simply inconvenience the investigator.

Comprehension

The manner and context, in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration, or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice. Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension. Special provision may need to be made, when comprehension is severely limited --for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill, and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose, to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected, both by acknowledging their own wishes, and by the use of third parties to protect them from harm. The third parties chosen should be those, who are most likely to understand the incompetent subject's situation, and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research, as it proceeds, in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness

An agreement to participate in research constitutes a valid consent, only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another, in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture, in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences, if the subject is especially vulnerable. Unjustifiable pressures usually occur, when persons in positions of authority or commanding influence --especially where possible sanctions are involved--urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely, where justifiable persuasion ends and undue influence begins. But undue influence would include actions, such as manipulating a person's choice through the controlling influence of a close relative, and threatening to withdraw health services to which an individual would otherwise be entitled.

Assessment of Risks and Benefits

The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits

The requirement that research be justified on the basis of a favorable risk / benefit assessment, bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm, and the severity (magnitude) of the envisioned harm. The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk", "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk / benefit assessments are concerned with the probabilities and magnitudes of possible harms, and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm, and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked. Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests, other than those of the subject, may on some occasions be sufficient by

themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects, and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits

It is commonly said that benefits and risks must be "balanced", and shown to be "in a favorable ratio". The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished, with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies. Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject --or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

Selection of Subjects

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk / benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients, who are in their favor, or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens, and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice, that there is an order of preference in the selection of classes of subjects (e.g., adults before children), and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions. Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators, and treated fairly in the course of research. Thus, injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if institutional review boards are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects. Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects, if more advantaged populations are likely to be the recipients of the benefits. One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized, may continually be sought as research subjects, owing to their ready availability in settings, where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

TICK-ASSOCIATED RASH STUDY

ADULT CONSENT/ PARENTAL PERMISSION/ ADOLESCENT ASSENT FORM

[NOTE: This form should be signed by patients 18 years of age or older who are able to give their legal consent. A parent or guardian of a minor child who is at least 3 years old should sign this form to give permission for the minor to enroll. Minor children ages 15-17 should sign this form to give their assent when a parent or guardian has given permission to enroll.]

Introduction Each year, the Centers for Disease Control and Prevention (CDC) hears of a mild illness that is a red, spreading skin rash. It occurs after tick bite in people living in the south or southeastern United States. These skin rashes usually look like the "bull's eye" rash of Lyme disease. The germs that cause Lyme disease do not seem to cause the rash in the South. However, related germs might cause such infections. One of these related germs is named *Borrelia lonestari.* We will test for this germ and other germs as these tests become available during this study. The CDC Institutional Review Board will approve of tests for other germs before they are performed on your samples. Your doctor has asked you/your child to be in this research study because you/your child has a skin rash that may have come after a tick bite. The CDC is working with local doctors to do this research study. The CDC expects about 60 persons to be in this study over a period of three years.

Purpose The purpose of this study is to find the cause of the red, spreading skin rash that sometimes follows a tick bite in people living in the southern United States.

Procedures Your doctor will ask you/your child for two skin samples from the rash site. You/your child would not usually give skin samples to your doctor for your illness. The skin samples are only for this study. Your doctor also will ask you/your child for a blood sample. If the rash is no longer there, your doctor will ask you/your child for only a blood specimen.

a. **Blood** A physician, nurse, or medical technologist will take about 3 teaspoons of blood from your arm/your child's arm at the first visit to your doctor's office. They will take a second sample of about 2 teaspoons of blood 3 to 6 weeks later. Please make an appointment at your clinic today to schedule this second blood sampling. If you miss this second appointment, you will be called at home by a person from the clinic to reschedule it.

b. **Skin biopsy** A doctor will remove two small (less than 1/10 of an inch), round pieces of skin. The tool used to take a skin sample is sterile (free of germs) and disposable. The procedure for removing skin is called a punch biopsy. This is a standard minor medical procedure. The doctor will give two small, separate shots of a local pain killer with a needle just under the skin before the biopsy. Although these shots will reduce the pain from the biopsy, there still may be some discomfort during the procedure.

You/your child may participate in this study by giving only blood. You/your child may decide to give one skin sample instead of two.

The CDC will test your samples for signs of germs that might cause your/your child's rash. Your doctor may request testing for Lyme disease. The CDC will do these tests, if asked, and report only the results of Lyme disease tests to your doctor.

Long Term Storage of Specimens

After these initial tests have been performed, the CDC will store samples that are left in a confidential manner for future testing. After this study is over, CDC may do new tests for germs that might have caused your/your child's rash as these tests become available. The CDC will not report the results of these tests to your doctor or to you. CDC will not do human genetic testing or test for evidence of HIV (human immunodeficiency virus) infection of the samples that you or your child provide. If at a later date you change your mind, you may ask to remove these samples from long term storage and destroy them. If you choose to do so, please contact Dr. Barbara Johnson at the CDC at 970-221-6400.

Risks and Discomforts

a. **Blood drawing** Your doctor will take blood from your/your child's arm using a needle. Drawing the blood may hurt a little. It may also cause some bruising, bleeding, and slight soreness at the puncture site. There is a small chance you/your child could get germs in the spot where the blood was taken and become infected. If the area around the spot gets red and sore, you/your child would need to go to the clinic.

b. **Skin biopsy** You/your child will have slight pain, redness, bleeding, or bruising at the biopsy site. A tiny scar may form there later. Usually, you/your child will not need stitches. There is a small risk of infection at the biopsy site. You will be given an instruction sheet that will tell you/your child how to help the wound to heal quickly and what to do if it does not.

Benefits You/your child will not directly benefit from the study. There is a benefit to society in general, through finding the cause of skin rash illness after tick bites in the southern United States.

Confidentiality The CDC will keep the data collection, informed consent/permission and assent forms in a locked file. Only study staff will be allowed to look at them. The CDC will keep the forms private as much as legally possible. To protect your/your child's privacy, we will keep records and samples under code numbers rather than by name. However, we will maintain a link between code numbers and the forms that we keep in locked files. Your/your child's name or other facts that might point to you/your child will not appear when we present this study or publish its results.

Costs/Compensation You will be responsible for the routine medical costs from your/your child's visit. These are costs that you would have if you/your child were not in the research study. You will have no charge for collection of blood samples (now and in 3 to 6 weeks) and skin samples. You will not pay for the research tests that CDC will do on these samples. If you are hurt as a result of being in this study, treatment will be provided by your health care provider. CDC does not normally pay for harm done to you as a result of being in a research study. Thus, you (or your insurer, Medicare, or Medicaid) will have to pay for any care that is needed.

Right to Refuse or Withdraw You/your child does not have to be in this study. Your doctor will give you/your child the usual care for your/your child's condition whether or not you/your child are in the study, or if you/your child leave the study later. To leave the study, please contact your doctor. You/your child may leave the study at any time.

Persons to Contact By signing this consent form and agreeing to be in this study, you are not giving up any of your rights. If you believe that you/your child have been harmed, please contact the Deputy Associate Director of Science at 1-800-584-8814 for information on your rights and advice on how to proceed. If the Deputy Director does not answer directly, leave a message including your name and phone number and protocol number 4278, so that you may be called back as soon as possible. The Deputy Director is not affiliated with this study in any way. If you have any questions, comments, or

complaints about this study, please write or call Dr. Barbara J. B. Johnson, Bacterial Zoonoses Branch, Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention, P.O. Box 2087, Fort Collins, Colorado 80522, (970) 221-6400. If you decide at a later date that you wish to have your/your child's sample(s) destroyed, call Dr. Johnson.

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I have checked the boxes for the parts of the study that I agree to for myself or for my child:

☐ Provide a blood sample today or as soon as possible

☐ Provide a second blood sample in 3-6 weeks

☐ Provide one skin sample from rash site today or as soon as possible

☐ Provide a second skin sample at the same time as the first sample

☐ Permit long-term storage and future testing of all samples (this is a requirement of enrollment)

Date_____ / _____ / _____

Please print _____
(Full name of patient or parent/guardian)

Address _____
Street City State Zip Code

Signature of patient or parent/guardian_____

Patient copy

TICK-ASSOCIATED RASH STUDY

ADULT CONSENT/ PARENTAL PERMISSION/ ADOLESCENT ASSENT FORM

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Date_____ / _____ / _____

Please print _____
(Full name of patient or parent/guardian)

Address _____
Street City State Zip Code

Signature of patient or parent/guardian_____

CDC copy

TICK-ASSOCIATED RASH STUDY

ASSENT FORM FOR MINORS 7-14 YEARS OLD

[NOTE TO PARENTS OR GUARDIANS: Children may enroll in this research study if you give permission. Before giving permission, please discuss this study with your child. To give permission, you must sign the ADULT CONSENT/ PARENTAL PERMISSION/ ADOLESCENT ASSENT form. If your child understands and agrees to be in this study and is between 7 and 14 years old, ask him or her to sign this form.

If your child is between 15 and 17 years old, both you and your child should sign ADULT CONSENT/ PARENTAL PERMISSION/ ADOLESCENT ASSENT FORMs. If your child is younger than 7, do not ask him or her to sign any form. Your written consent is sufficient.]

We are trying to find out why you got a rash. This is a research study. Your parent or guardian has said that it is all right to be in this study. If you say "yes", we would like to take a small amount of blood from your arm. You will feel a sharp pinch. We would also like to take two small pieces of skin from your rash. We will numb the skin first. This is so that it will not hurt too much. This place might hurt a little bit for a day or two afterwards. After 3 to 6 six weeks, we would like you to return to this clinic. We will take another small blood sample at this time.

You do not have to say "yes." If you say "no," your doctor will still take care of your rash. Do you have questions? Ask your mother or father or guardian. You also can ask your doctor.

I agree to take part in this study.

Please print _____ Date_____ / _____ / _____
(full name of minor patient)

Address _____
Street City State Zip Code

Signature of minor patient _____

TICK-ASSOCIATED RASH STUDY

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Please print _____ Date_____ / _____ / _____
(full name of minor patient)

Address _____
Street City State Zip Code

Signature of minor patient _____

LABORATORY SUBMISSION FORM FOR SOUTHERN TICK-ASSOCIATED RASH ILLNESS (STARI) SPECIMENS
CENTERS FOR DISEASE CONTROL AND PREVENTION

PLEASE DO NOT INCLUDE PATIENT'S NAME

PATIENT'S AGE _____ SEX Male Female DATE FORM COMPLETED _____ / _____ / _____
Mo Day Year

SPECIMEN TYPE	DATE OF COLLECTION	ANATOMIC LOCATION	CDC USE ONLY (ID Number, Date Rec'd)
SKIN			
RASH BIOPSY, fresh (A)	_____ / _____ / _____	_____	_____
RASH BIOPSY, fixed (B)	_____ / _____ / _____	_____	_____
BLOOD			
ACUTE WHOLE BLOOD	_____ / _____ / _____	n/a	_____
ACUTE SERUM	_____ / _____ / _____	n/a	_____
CONVALESCENT SERUM	_____ / _____ / _____	n/a	_____

OFFICE SUBMITTING SPECIMEN (Physician)

NAME_____ TELEPHONE (_____)_____

ADDRESS

_____
(Street) (City) (State) (Zip code)

1. What was the patient's **first sign or symptom**? _____

2. **Date of onset** of the first symptom _____ / _____ / _____

3. Does or did the patient have **elevated body temperature**? __ Measured ___^{o}F. Date measured ___/___/____

4. Does or did the patient have a **rash**? _____ Date of onset ____ / ____ / _____ Rash location _____
(e.g. hand, forearm, calf, shoulder, neck)

5. If a rash was present, please describe it. Include **maximum diameter** in centimeters **observed by physician**. Please submit a **photograph or draw a picture** of the rash on the back of this form.

_____

6. **Other** clinical signs or symptoms _____

7. Did the patient have any **exposure to ticks** in the **2 weeks prior** to this illness?
   - _____ yes, tick still attached (please save tick and submit it along with clinical specimens)
   - _____ yes, tick was reportedly attached
   - _____ yes, but tick was not attached
   - _____ yes, but tick attachment status not known
   - _____ no
   - _____ not known

   If yes, **where** did exposure to ticks occur?_____
   County State Country (if other than U.S.)

8. What medication(s) were prescribed for this patient?

MEDICATION	DATE STARTED	DOSE	ROUTE
_____	_____	_____	PO IM IV
_____	_____	_____	PO IM IV
_____	_____	_____	PO IM IV

9. **Current clinical status** Recovered Remains ill Unknown (CIRCLE ONE)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control and Prevention (CDC)
National Center for Infectious Diseases
Atlanta, Georgia 30333

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Reset Form

STUDY ID: _____ STATE CONTACT PERSON & PHONE NO.: _____

(for CDC Use Only)
CDC LAB. CODE | CDC NUMBER | DATE RECEIVED Mo. Da. Yr.

Justification must be completed by State health department laboratory before specimen can be accepted by CDC. Please check the first applicable statement and when appropriate complete the statement with the.*

1. Disease suspected to be of public health importance. Specimen is:
   (a) ☐ from an outbreak.
   (b) ☐ from uncommon or exotic disease.
   (c) ☐ an isolate that cannot be identified, is atypical, shows multiple antibiotic resistance, or from a normally sterile site(s)
   (d) ☐ from a disease for which reliable diagnostic reagents or expertise are unavailable in State.
2. ☐ Ongoing collaborative CDC/State project.
3. ☐ Confirmation of results requested for quality assurance.

*Prior arrangement for testing has been made. Please bring to the attention of:
(name) _____

Name, Address and Phone Number of Physician or Organization:

STATE HEALTH DEPT. NUMBER: _____ STATE LOC: _____

DATE SENT TO CDC: Mo. Da. Yr. _____ Completed by: _____

Patient Name: _____

PATIENT IDENTIFICATION NUMBER: _____

Have specimens from this patient been submitted previously ☐ YES ☐ NO

BIRTHDATE OR AGE _____ Mo. Da. Yr. _____ SEX: ☐ M ☐ F

RACE: White ☐ Black ☐ Asian or Pacific Islander ☐ American Indian or Alaska Native ☐ Not Specific ☐

ETHNICITY: Hispanic ☐ Non-Hispanic ☐ Not Specific ☐

CLINICAL DIAGNOSIS: _____

ASSOCIATED ILLNESS: _____

DATE OF ONSET: Mo. Da. Yr. _____ FATAL? ☐ YES ☐ NO

LABORATORY EXAMINATION REQUESTED:
☐ **AN**timicrobial Susceptibility ☐ **ID**entification ☐ **IS**olation
☐ **HI**stology ☐ **OT**her (Specify) _____
☐ **SE**rology (Specific Test) _____

CATEGORY OF AGENT SUSPECTED:
☐ **BA**cterial ☐ **VI**ral ☐ **FU**ngal ☐ **RI**ckettsial
☐ **PA**rasitic ☐ **OT**her (Specify) _____

SPECIFIC AGENT SUSPECTED: _____

OTHER ORGANISM(S) FOUND: _____

ISOLATION ☐ YES ☐ NO | **NO. TIMES ISOLATED:** _____

SPECIMEN SUBMITTED IS: ☐ **O**riginal **M**aterial ☐ **P**ure **I**solate ☐ **M**ixed **I**solate

DATE SPECIMEN TAKEN: Mo. Da. Yr. _____

ORIGIN: ☐ **SO**il ☐ **FO**od ☐ **AN**imal (Specify) _____
☐ **HU**man ☐ **OT**her (Specify) _____

SOURCE OF SPECIMEN:
☐ **BL**ood ☐ **SE**rum ☐ **CSF** ☐ **ST**ool ☐ **SP**utum
☐ **UR**ine ☐ **GA**stric ☐ **HA**ir ☐ **SK**in ☐ **TH**roat
☐ **WO**und (Site) _____
☐ **EX**udate (Site) _____
☐ **TI**ssue (Specify) _____
☐ **OT**her (Specify) _____

SUBMITTED ON:
☐ **EG**g ☐ **TI**ssue Culture (Type) _____
☐ **AN**imal (Specify) _____
☐ **ME**dium (Specify) _____
☐ **OT**her (Specify) _____

SERUM INFORMATION: Mo. Da. Yr. _____ Mo. Da. Yr. _____
☐ **AC**ute ☐ **S3**

IMMUNIZATIONS: Mo. Da. Yr.

TREATMENT: Drugs Used: DATE BEGUN Mo. Da. Yr. DATE COMPLETED Mo. Da. Yr.

CLINICAL TEST RESULTS:
Sputum and Histological Findings: _____
Blood Counts: _____ Stool/Urine Exams: _____
Type Skin Tests Performed: Mo. Da. Yr. Strength Pos. Neg.

SIGNS AND SYMPTOMS:
☐ **FE**ver
Maximum Temperature: ____
Duration: _____ Days
☐ **CH**ills

SKIN:
☐ **MA**culopapular
☐ **HE**morrhagic
☐ **VE**sicular
☐ **E**rythema **N**odosum
☐ **E**rythema **M**arginatum
☐ **OT**her _____

RESPIRATORY:
☐ **RH**initis
☐ **PU**lmonary
☐ **PH**aryngitis
☐ **CA**lcifications
☐ **O**titis **M**edia
☐ **PN**eumonia (type)_____
☐ **OT**her _____

CARDIOVASCULAR:
☐ **MY**ocarditis
☐ **PE**ricarditis
☐ **EN**docarditis
☐ **OT**her _____

GASTROINTESTINAL:
☐ **DI**arrhea
☐ **BL**ood
☐ **MU**cous
☐ **CO**nstipation
☐ **AB**normal Pain
☐ **VO**miting
☐ **OT**her _____

CENTRAL NERVOUS SYSTEM:
☐ **HE**adache
☐ **ME**ningismus
☐ **MI**crocephalus
☐ **HY**drocephalus
☐ **SE**izures
☐ **CE**rebral Calcification
☐ **CH**orea
☐ **PA**ralysis
☐ **OT**her _____

MISCELLANEOUS:
☐ **JA**undice
☐ **MY**algia
☐ **PL**eurodynia
☐ **CO**njunctivitis
☐ **CH**orioretinitis
☐ **SP**lenomegaly
☐ **HE**patomegaly
☐ **L**iver **A**bscess/cyst
☐ **LY**mphadenopathy
☐ **MU**cous Membrane Lesions
☐ **OT**her _____

STATE OF ILLNESS:
☐ **SY**mptomatic
☐ **AS**ymptomatic
☐ **SU**bacute
☐ **CH**ronic
☐ **DI**sseminated
☐ **LO**calized
☐ **EX**traintestinal
☐ **OT**her _____

EPIDEMIOLOGICAL DATA:
☐ **SI**ngle Case ☐ **SP**oradic ☐ **CO**ntact ☐ **EP**idemic ☐ **CA**rrier

Family Illness: _____
Community Illness: _____

Travel and Residence (Location): Mo. Da. Yr.
☐ **Foreign:** _____
☐ **USA:** _____

Animal Contacts (Species): _____
Arthropod Contacts: ☐ **NO**ne ☐ **EX**posure Only ☐ **BI**te
Type of Arthropod: _____
Suspected Source of Infection: _____

PREVIOUS LABORATORY RESULTS/OTHER CLINICAL INFORMATION:
(Information supplied should be related to this case and/or specimen(s) and relative to the test(s) requested.

The types of specimens usually sent to CDC laboratories are serum specimens, reference cultures, or clinical specimens. To assist State health department laboratories and others in obtaining the information on the request form that NCID requires, the following tabulation for each of the 3 types of specimens should serve as a guide.

SERUM SPECIMENS

Required	Useful
Laboratory exam requested	Clinical information
Specific agent suspected	Signs, symptoms, etc.
Serum information*	
Immunization*	
Treatment*	
Epidemiologic data*	
Previous lab results	

REFERENCE CULTURES

Required	Useful
Laboratory exam requested	Isolation attempted
Category of agent suspected	Date specimen taken
Specific agent suspected	Number times isolated
Kind of specimen	Other clinical information
Origin of specimen	Clinical test results
Source of specimen	Signs, symptoms, etc.
Submitted on what medium	Other organisms found**
Previous lab results	Epidemiologic data*
Biochemical reaction (can be attached on a separate sheet)	Treatment*

CLINICAL SPECIMENS

Required	Useful
Laboratory exam requested	Other clinical information
Category of agent suspected	Clinical test results
Specific agent suspected	Signs, symptoms, etc.
Specimen submitted is	
Date specimen taken	
Source of specimen	
Epidemiologic data*	
Previous lab results	

The Reference and Disease Surveillance Booklet should be consulted for special requirement.

**Exercise good judgement to determine the relevance of these items.* Paired sera are required for viral and bacterial disease serology, a single serum is required for mycotic and parasitic diseases and for syphilis serology (congenital syphilis excepted). In all instances the date(s) of collection of serum specimens must be provided. Immunization history is required when such information relates to the serology requested, i.e., required for polio, measles, etc., not required for histoplasmosis, echinococcosis, etc. Information on treatment, such as administration of immune serum or globulin, antibiotics, etc., is often of great benefit when doing serology or identifying reference cultures. As much relevant epidemiologic data as can be obtained should be provided. History of travel and animal or arthropod contacts are required for those RDS in which this kind of information is clearly necessary. If any required item of information is not available after efforts have been made to obtain it, please so indicate.

**Bacterial cultures representing growth of a single or a few colonies on the same primary isolation agar plates from which the principal pathogen has been isolated and identified should not be submitted for identification unless clinical findings or other justification support such submissions.

Print

Shipping Instructions

1. In the large styrofoam box with gel ice packs place
   Skin biopsy specimen in PBS transport medium
   Skin biopsy specimen (if any) in fixative
   Whole blood, lavender cap/EDTA tube
   Acute-phase serum sample in red/gray top Corvac or Vacutainer tube

   Hold blood samples and skin (in PBS) in a refrigerator until they are shipped.
   Ship all samples cooled by ice packs. Use air bill provided by CDC for FedEx.

2. In the small styrofoam box with gel-ice pack packs place
   Convalescent-phase blood sample

   Collect convalescent-phase sample 3-6 weeks after acute-phase sample.
   Hold this sample in a refrigerator until it is shipped. Ship sample cooled by ice packs.
   Use the second air bill provided for FedEx.

Notes

Each specimen kit contains:

One 1.5-ml screw cap tube labeled PBS (phosphate-buffered saline) for skin biopsy sample

One 1.5-ml screw cap tube labeled Fixative for a second rash skin biopsy sample
   This tube contains Streck's tissue fixative.
   Only use this tube if you have more than one skin biopsy sample from a rash

One lavender top tube for un-coagulated whole blood

Two red/gray top tubes for serum
   One tube is for an acute-phase sample
   The other tube is for a convalescent-phase sample
   Centrifuge blood and refrigerate it until shipment

Two AcuPunch skin biopsy punches (2 mm diameter)
   Sample to depth of 3-4 mm

Vacutainer needles

Gel-ice packs for shipping